Comparative Study of Selected Disintegrating Agents

By WILLIAM FEINSTEIN* and ANDREW J. BARTILUCCI

Five tablet disintegrants were evaluated using 2 especially formulated bases alone and with active ingredients. The test tablet bases included a highly soluble formulation and an insoluble one. The materials evaluated were Veegum WG, Solka Floc BW-200, Jaguar A-20-B, Purity 825 cornstarch, and Landalgine P. An evaluation of the latter 2 previously was unreported. Purity 825 cornstarch and Jaguar A-20-B at 10 per cent levels were found to be the most effective. No significant change in disintegration time was noted upon the incorporation of a low concentration of an active ingredient, or upon the incorporation of a high concentration of a soluble medicament.

COMPRESSED tablets afford a convenient method for administering drugs. Most compressed tablets are formulated so as to contain fillers, binding agents, lubricants, and disintegrating agents, in addition to the active medicament. Excluding the disintegrating agent, the aforementioned components contribute chiefly to the smooth machine operation in the preparation of the finished compressed tablet. Fillers provide for a convenient tablet size and/or carrier for small amounts of active ingredients. Binding agents bring about a cohesive bond between the particles. Lubricants reduce friction and thereby permit the free flow of the granulation through the hopper and the ready ejection of the tablet from the die. It is the function of the disintegrating agent to cause the compressed tablet to break apart or disintegrate when in the presence of fluids to allow for a more favorable condition for the absorption of the contained medicament.

The literature is replete with reports pertaining to the evaluation of disintegrating agents under a variety of conditions. Factors influencing disintegration time include mechanical apparatus, materials, formulations, and techniques employed (1, 2). Several investigators (1, 3, 4) used cornstarch in the base formulation as a filler and/or binder. Kwan *et al.* (4) and Krebs (5) reported that cornstarch, when used as a filler and binder, caused significant changes in tablet disintegration times. Other investigators (6–8) reported the mutually potentiating effect of cornstarch when combined with other disintegrating agents or with substances that are capable of influencing the disintegration time of compressed tablets. Therefore, in an evaluation of disintegrating agents, the disintegration time values obtained when cornstarch is used as a binder or filler are not truly comparative representations of the disintegrating agent's ability. A more valid approach in evaluating disintegrating agents would involve the formulation of a granulation or base formula containing ingredients that did not in themselves act as disintegrating agents.

Employing a variety of active ingredients, the amounts of which were selected because they produced satisfactory tablets, many investigators (3, 7, 9–17) reported that these had an effect on disintegration time.

One objective of this investigation was the evaluation of representative disintegrating agents from each of the most commonly used chemical categories of disintegrants utilizing base formulations containing ingredients that did not themselves possess disintegrating properties. Disintegrating agents may be chemically classified as starches, clays, celluloses, algins, and gums. Two substances from the starch and algin categories, Purity 825 cornstarch and Landalgine P, respectively, not reported previously were included. Furthermore, the effect on disintegration time of 3 representative types of active ingredients present in realistic quantities was to be determined.

EXPERIMENTAL

Materials Used.—The chemicals employed were of U.S.P. or N.F. quality, or were offered by the manufacturer for drug use. The representative disintegrators were selected from several in each of the chemical categories on the basis of superior performance in preliminary experimental batches utilizing an aspirin granulation. The agents tested included: cornstarch U.S.P. and Purity 825[1] (a low moisture cornstarch) as representative of starches; Solka Floc[2] BW-40 and BW-200, Avicel,[3] and Methocel[4] MC 400 cps. as representative of celluloses; Jaguar[5] (guar gum) A-20-B and A-20-D as representative of gums; Landalgine[6] P and Kelacid[7] as representative of algins; and Veegum[8] (magnesium

Received October 25, 1965, from the Department of Pharmaceutical Sciences, St. John's University, Jamaica, N. Y.
Accepted for publication December 1, 1965.
Abstracted from a thesis submitted by William Feinstein to the Graduate School, St. John's University, Jamaica, N. Y., in partial fulfillment of Master of Science degree requirements.
* Present address: NYSCO Laboratories, Inc., Long Island City, N. Y.

[1] National Starch and Chemical Co., N. Y.
[2] Brown Co., N. Y.
[3] American Viscose Corp., Pa.
[4] Dow Chemical Corp., N. Y.
[5] Stein, Hall and Co., N. Y.
[6] E. Mendell Co., N. Y.
[7] Kelco Co., N. J.
[8] R. T. Vanderbilt Co., N. Y.

TABLE I.—BASE FORMULATIONS

Ingredients	Wt., Gm. Base LS			Base HS		
Calcium sulfate, dihydrate	778.5	756.0	711.0	...	...	...
Lactose	...	...	...	508.5	486.0	441.0
Sucrose	...	...	...	270.0	270.0	270.0
Acacia	90.0	90.0	90.0	90.0	90.0	90.0
Calcium stearate	9.0	9.0	9.0	9.0	9.0	9.0
Disintegrating agent	22.5	45.0	90.0	22.5	45.0	90.0
(%)	(2.5)	(5.0)	(10.0)	(2.5)	(5.0)	(10.0)

TABLE II.—AVERAGE DISINTEGRATION TIME (min.) OF TABLETS OF BASE FORMULATIONS AND DISINTEGRANTS

Disintegrants	Base LS[a] 2.5%	5.0%	10.0%	Base HS[a] 2.5%	5.0%	10.0%
Purity 825 cornstarch	24.5	19.0	16.0	11.5	10.0	9.5
Jaguar A-20-B	22.5	19.0	17.0	14.0	11.0	9.0
Veegum WG	39.0	29.0	37.0	12.5	10.5	15.0
Solka Floc BW-200	35.5	30.0	32.0	12.0	11.0	16.0
Landalgine P	30.0	28.5	29.5	11.0	9.5	10.5

[a] Tablets prepared from the base formulations without the addition of disintegrating agents yielded an average disintegrating time of 44 min. for base LS and an average time of 14.5 min. for base HS.

TABLE III.—FORMULATIONS OF PREDNISONE AND BASE FORMULATION MATERIALS

Ingredients	Wt., Gm. Base LS		Base HS	
Prednisone	10.0	10.0	10.0	10.0
Calcium sulfate, dihydrate	746.0	701.0	...	...
Lactose	...	...	476.0	431.0
Sucrose	...	...	270.0	270.0
Acacia	90.0	90.0	90.0	90.0
Calcium stearate	9.0	9.0	9.0	9.0
Disintegrating agent	45.0	90.0	45.0	90.0
(%)	(5.0)	(10.0)	(5.0)	(10.0)

TABLE IV.—FORMULATIONS OF SODIUM SULFADIAZINE AND SULFADIAZINE AND BASE FORMULATION MATERIALS

Ingredients	Wt., Gm. Base LS		Base HS	
Sulfa drug	600.0	600.0	600.0	600.0
Calcium sulfate, dihydrate	156.0	111.0	...	...
Lactose	...	...	106.0	81.0
Sucrose	...	...	50.0	30.0
Acacia	90.0	90.0	90.0	90.0
Calcium stearate	9.0	9.0	9.0	9.0
Disintegrating agent	45.0	90.0	45.0	90.0
(%)	(5.0)	(10.0)	(5.0)	(10.0)

aluminum silicate) F and WG as representative of clays. Those included in the study of this report appear in Table II. The tableting properties of Purity 825 cornstarch and Landalgine P do not appear in the literature.

Development of Base and Test Formulations.—Two base formulations were sought that would yield a uniformly granular material of sufficient hardness that could be readily tableted, have significantly different disintegrating times and solubilities, and be free of materials that would contribute to the disintegration of the tablet by swelling when moist. Experimental batches of tablet granulations were prepared and tested. The 2 base formulations finally selected appear in Table I, with the concentration of each ingredient and the concentration of disintegrating agent utilized at each percentage level. The formulations produced uniform granulations which had a minimum of fines and tableted readily. Base LS formulations contained ingredients of low solubility while base HS formulations contained more soluble ingredients. The disintegrating agents were incorporated with the base formulations at concentrations of 2.5, 5.0, and 10.0%. Disintegrating agents at the 5.0 or 10.0% level were selected for formulation with the active medicaments, prednisone, sulfadiazine, and sodium sulfadiazine (Tables III and IV). The concentration of disintegrant represented the most effective level from Table II. The concentration of active ingredient incorporated in the formulation represented a realistic therapeutically prescribed amount. Thus, prednisone tablets were studied at the 5 mg. level and the sulfa drugs at the 300 mg. level. Disintegration times of tablets containing active ingredients appear in Table V.

TABLE V.—AVERAGE DISINTEGRATION TIME (min.) OF TABLETS CONTAINING ACTIVE MEDICAMENTS, BASE FORMULATION MATERIALS, AND DISINTEGRANTS

Disintegrants	Prednisone Base LS	Prednisone Base HS	Sulfadiazine Base LS	Sulfadiazine Base HS	Sodium Sulfadiazine Base LS	Sodium Sulfadiazine Base HS
Purity 825, 10%	15.5	9.0	78.0	69.0	9.5	9.0
Jaguar A-20-B, 10%	15.0	8.5	41.0	36.0	9.0	8.0
Veegum WG, 5%	27.5	11.0	90.0	88.0	10.5	9.5
Solka Floc BW-200, 5%	29.0	13.0	>100	98.0	11.5	10.0
Landalgine P, 5%	26.0	9.5	>100	95.0	15.0	12.5

Table VI.—Gross Appearance[a] of Tablet Surface

	Purity 825	Jaguar A-20-B	Veegum WG	Solka Floc BW-200	Landalgine P
Base LS—2.5% dis. agent	+/+	+/+	+/+	+/+	+/+
5.0% dis. agent	+/+	+/+	+/+	+/+	+/+
10.0% dis. agent	+/+	−/+	+/+	+/+	+/+
Base HS—2.5% dis. agent	+/+	+/+	+/+	+/+	+/+
5.0% dis. agent	+/+	+/+	+/+	+/+	+/+
10.0% dis. agent	+/+	−/+	+/+	+/+	+/+
Prednisone–base LS	+/+	+/+	+/+	+/+	+/+
Prednisone–base HS	+/+	+/+	+/+	+/+	+/+
Sulfadiazine–base LS	+/+	−/+	−/+	+/+	+/+
Sulfadiazine–base HS	+/+	−/+	−/+	−/+	−/+
Sodium sulfadiazine–base LS	+/+	−/+	+/+	+/+	+/+
Sodium sulfadiazine–base HS	+/+	−/+	+/+	+/+	+/+

[a] Whiteness/uniformity of appearance: −, off-white or mottled; +, white or nonmottled.

Manufacturing and Testing Procedures.—The powders were blended and passed through a No. 40 mesh screen. Purified water was added, and the mass was granulated by hand. The wet mass was forced through a No. 8 mesh screen, spread on trays, and dried in an oven at 38° for 14 hr. The dried granulation was forced through a No. 14 mesh screen. The fines smaller than No. 40 mesh were separated. The lubricating and disintegrating agents were mixed and passed through a No. 80 mesh screen and then blended with the granulation fines. These fines were incorporated in the granulation, and the granulation was compressed.

In the preparation of the prednisone tablets, the medicament was mixed with the fines, and these were incorporated into the granulation. The sulfadiazine tablets and the sodium sulfadiazine tablets were prepared by mixing the medicament with the filler before wet granulating. Two thousand tablets per batch were compressed on a Colton 216 rotary tablet machine utilizing $^{13}/_{32}$-in. standard concave punches and dies. The weight of each tablet was maintained at 450 ± 5 mg., and the hardness, as measured on the Stokes hardness tester, at 5 to 7 ± 0.5 Kg.

The disintegration tests were performed soon after compression using the U.S.P. (18) apparatus and method for uncoated tablets. In addition, formulations containing the active medicaments were reexamined after a minimum of 5 months' storage at room temperature. Test tablets were selected at random from each batch. Three determinations were made for each batch.

RESULTS AND DISCUSSION

It is often assumed that the disintegration time may be decreased by increasing the concentration of disintegrant. The results in Table II show this to be the case with Purity 825 cornstarch and Jaguar A-20-B. A concentration level for optimum effectiveness appears to apply with Veegum WG, Solka Floc BW-200, and Landalgine P, albeit the data are too limited to be definitive. The most effective disintegrants in the formulations studied were Purity 825 cornstarch and Jaguar A-20-B at 10% levels.

A study of Tables II and V reveals that no significant change in disintegration time occurred upon the incorporation of a low concentration of the active ingredient, prednisone, nor upon the incorporation of a high concentration of the soluble active ingredient, sodium sulfadiazine. The inclusion of a high concentration of the insoluble active ingredient, sulfadiazine, markedly increased the disintegration time of the tablets.

No significant change in disintegration time or tablet hardness was observed after storage at room temperature for 5 months.

To provide additional comparative information on the previously unreported Landalgine P and Purity 825 cornstarch, a description of the gross appearance of finished tablets appears in Table VI.

REFERENCES

(1) Ward, J. B., and Trachtenberg, A., *Drug Cosmetic Ind.*, **91**, 35(1962).
(2) Gross, H. M., and Becker, C. H., *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 157(1952).
(3) Perlman, K. P., Banker, G. S., and DeKay, H. G., *Drug Cosmetic Ind.*, **94**, 660(1964).
(4) Kwan, K. C., Swart, F. O., and Mattocks, A. M., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 236(1957).
(5) Krebs, V. C., *Anales Chim. Farm. Univ. Chile*, **11**, 204(1959); through *Chem. Abstr.*, **54**, 25575(1960).
(6) Cooper, B. F., and Brecht, E. A., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 520(1957).
(7) Crisafi, R. C., and Becker, C. H., *ibid.*, **47**, 363(1958).
(8) Fakouhi, T. A., Billups, N. F., and Sager, R. W., *J. Pharm. Sci.*, **52**, 700(1963).
(9) Firouzabadian, A., and Huyck, C. L., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 248(1954).
(10) Bequette, R. J., and Huyck, C. L., *Drug Cosmetic Ind.*, **81**, 166(1957).
(11) Berry, H., and Ridout, C. W., *J. Pharm. Pharmacol.*, **2**, 619(1950).
(12) Eatherton, L. E., Platz, P. E., and Cosgrove, F. P., *Drug Std.*, **23**, 42(1955).
(13) Gerding, T. G., and DeKay, H. G., *ibid.*, **23**, 132 (1955).
(14) Granberg, C. B., and Benton, B. E., *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 648(1949).
(15) Nait, A. D., and Bhatia, V. N., *ibid.*, **46**, 131(1957).
(16) Shah, R. H., and Huyck, C. L., *Drug Cosmetic Ind.*, **86**, 336(1960).
(17) Van Abbé, N. J., and Rees, J. T., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 487(1958).
(18) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 934.